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Antecedents of New-Onset Major Depressive Disorder in Children and Adolescents at High Familial Risk

Frances Rice, PhD; Ruth Sellers, PhD; Gemma Hammerton, PhD; Olga Eyre, MD; Rhys Bevan-Jones, MD; Ajay K. Thapar, PhD, MD; Stephan Collishaw, PhD; Gordon T. Harold, PhD; Anita Thapar, PhD, MD

IMPORTANCE Early-onset major depressive disorder (MDD) is common in individuals at high familial risk of depression and is associated with poor long-term mental health, social, and educational outcomes.

OBJECTIVES To examine the developmental pathways that lead to first-episode adolescent-onset MDD (incident cases) in those at high familial risk and to postulate a theoretically informed model that enables simultaneous testing of different pathways to incident adolescent-onset MDD composed of contributions from familial/genetic and social risk factors, as well as effects via specific clinical antecedents.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a 4-year longitudinal study (April 2007 to March 2011) among offspring of depressed parents in the general community. Analyses were conducted between September 1, 2015, and May 27, 2016. Participants were 337 families in whom the index parent (315 mothers and 22 fathers) had experienced at least 2 episodes of MDD (recruited through primary care) and among whom there was a biologically related child in the age range of 9 to 17 years living with the index parent (197 girls and 140 boys with a mean [SD] age of 12.4 [2.0] years) at baseline. Offspring with MDD before the study or at baseline ($n = 27$), offspring with an episode of MDD that had remitted by follow-up ($n = 4$), and offspring with missing baseline MDD data ($n = 2$) were excluded. Ninety-two percent (279 of 304) of families completed the follow-up.

MAIN OUTCOMES AND MEASURES The primary outcome was new-onset offspring MDD, and the secondary outcome was the total *DSM-IV* MDD symptom score.

RESULTS On average, children and adolescents had a mean (SD) of 1.85 (1.74) (range, 0-8.5) *DSM-IV* symptoms of MDD at follow-up. Twenty (6 males and 14 females) had new-onset MDD, with a mean (SD) age at onset of 14.4 (2.0) years (range, 10-18 years). Irritability ($\beta = 0.12$, $P = .03$) and fear and/or anxiety ($\beta = 0.38$, $P < .001$) were significant independent clinical antecedents of new adolescent-onset MDD, but disruptive behavior ($\beta = -0.08$, $P = .14$) and low mood ($\beta = -0.03$, $P = .65$) were not. The results were similar for the *DSM-IV* symptom count at follow-up. All the measured familial/genetic and social risk indicators directly influenced risk for new-onset MDD rather than indirectly through acting on dimensional clinical antecedents.

CONCLUSIONS AND RELEVANCE There are multiple pathways to first-onset adolescent depression in individuals at familial risk. Irritability and fear/anxiety may be additional clinical phenomena to be included as targets in primary preventive interventions focusing on the child. In addition to targeting these phenomena in parents and children, depression prevention methods in high-risk groups may need to take into consideration social risks, such as poverty and psychosocial adversity.

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Author Affiliations: Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, Wales (Rice, Sellers, Hammerton, Eyre, Bevan-Jones, A. K. Thapar, Collishaw, A. Thapar); Rudd Centre for Adoption Research and Practice, School of Psychology, University of Sussex, Sussex, England (Sellers, Harold); School of Social and Community Medicine, University of Bristol, Bristol, England (Hammerton).

Corresponding Author: Frances Rice, PhD, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Maindy Road, Hadyn Ellis Bldg, Cardiff CF24 4HQ, Wales (ricef2@cardiff.ac.uk).

Major depressive disorder (MDD) is a leading global cause of lifelong disability. The incidence markedly rises during mid-adolescence,¹⁻³ and first onset at this age predicts a long-term trajectory of symptoms into adult life,⁴⁻⁶ with especially poor long-term mental health, social, and educational outcomes.^{2,4-7} Even when the onset of depression is in adult life, many of its contributing risk factors begin during childhood,^{8,9} highlighting the importance of understanding the etiology of early-onset MDD.¹⁰ The most common major risk factor for early-onset MDD is depression in a parent.^{6,11-13} Therefore, the adolescent offspring of depressed parents are an important group for investigating the initial development of early-onset MDD.

Major depressive disorder has a complex multifactorial etiology that includes inherited or familial influences¹³⁻¹⁸ and social risk factors.^{8,9,19,20} How do such risks collectively affect the child and eventually translate into first-onset MDD? The childhood symptom dimensions of fear and/or anxiety, depression (low mood), and conduct and oppositional problems have been found to precede later mood disorder.²¹⁻²⁶ Irritability may be a distinct dimension of oppositional behavior that independently predicts depressive symptoms.²⁷⁻²⁹ Therefore, familial/genetic and social risk factors may increase the probability of incident MDD through earlier effects on these symptom dimensions that appear to be antecedents to disorder.

Despite a consensus that depression has multifactorial causes and likely involves multiple risk pathways that begin in childhood, studies to date have documented elevated lifetime rates of depressive disorder in those at familial risk but have not tested which developmental processes are involved in the initial onset of MDD in these individuals. These data would be informative for refining primary prevention methods. Depression prevention efforts focus on modifying low mood, with promising results when prevention targets those at elevated risk for MDD, including offspring of depressed parents.³⁰⁻³² However, there are different developmental routes to first-onset MDD. If these channels can be identified, targeting relevant risk factors and clinical antecedents could be useful adjuncts to existing prevention programs.³³

A focus on identifying processes involved in the first onset of adolescent depression is warranted given the high rates of recurrence when depression arises at this time.⁴ To our knowledge, this article is the first to examine the antecedents of the initial onset of MDD during adolescence in a high-risk sample using an approach that models risk factors simultaneously and accounts for the co-occurrence of such risks. We set out to test whether multiple indicators of familial risk and social adversity simultaneously affect first-onset MDD via irritability, disruptive behavior, fear/anxiety, and low mood in a longitudinal study of high-risk child and adolescent offspring of parents with a history of recurrent MDD.

Methods

Participants

Data were from a prospective longitudinal study of the offspring of parents with recurrent depression. At baseline, there

Key Points

Question In individuals at high familial risk, what are the developmental pathways that lead to the first onset of major depressive disorder in adolescence?

Findings This investigation was a 4-year longitudinal study among offspring of depressed parents in the general community. In a theoretically informed model that simultaneously tested different pathways, irritability and fear and/or anxiety were the clinical antecedents of new-onset major depressive disorder, and social and familial risk factors directly affected new-onset major depressive disorder.

Meaning Depression prevention methods in high-risk groups likely need to target clinical phenomena in parents and children and take into consideration social risks, such as poverty and psychosocial adversity.

were 337 families (315 mothers and 22 fathers) recruited primarily from United Kingdom general practices.³⁴ The presence of at least 2 episodes of *DSM-IV* MDD in the index parent was confirmed at baseline with a timeline of the parent's previous depressive episodes,^{35,36} and the Schedules for Clinical Assessment in Neuropsychiatry³⁷ assessed current parental depression. One child per family was included. The youngest child between 9 and 17 years old was selected to reduce the likelihood that children had already experienced MDD, totaling 197 girls and 140 boys (mean [SD] age, 12.4 [2.0] years at baseline). All children were biologically related to and living with the affected parent. Additional exclusion criteria were moderate to severe intellectual disability (IQ, <50) in the child and the presence of *DSM-IV* criteria for bipolar disorder, mania or hypomania, or psychotic disorder in the parent at interview. Two families were excluded because the index parent was subsequently diagnosed as having bipolar disorder. Parents and offspring were assessed on 3 occasions. The mean (SD) time between the baseline (T1) and second (T2) assessment was 16.2 (2.6) months and between the second and third (T3) assessment was 12.5 (1.6) months. Data were collected via semistructured diagnostic interviews and questionnaires.³⁴ Written informed consent or assent was obtained from parents and children as appropriate. The Multi-Center Research Ethics Committee for Wales (of the National Health Service Health Research Authority) approved the study.

Outcome Variables at Follow-up

Primary Outcome of New-Onset Offspring MDD

Child psychopathologic conditions were assessed with the Child and Adolescent Psychiatric Assessment (CAPA),³⁸ which is a semistructured diagnostic interview that derives psychiatric symptoms and diagnoses during the preceding 3 months.^{38,39} The parent and child assessments were completed independently by trained, supervised interviewers. A modified section of the CAPA was used to collect information on MDD symptoms occurring before the study and between assessments. Major depressive disorder was defined as the presence of at least 5 depressive symptoms, including one of

the core symptoms of low mood or irritability or loss of interest plus depression-related impairment (assessed with the incapacity section of the CAPA).³⁸ Diagnosed and subthreshold cases were reviewed by 2 experienced child and adolescent psychiatrists (including one of us [A.T.]). The primary outcome was new-onset offspring MDD, defined as MDD at T2 or T3 assessment. To increase confidence that we were identifying first-onset MDD cases, we excluded offspring with a diagnosis of MDD before T1 or at T1 ($n = 27$), offspring with an episode of MDD that had remitted between follow-up assessments ($n = 4$), and offspring with missing MDD diagnostic information at baseline ($n = 2$). These exclusions resulted in a maximum sample of 304 families. Diagnostic data at follow-up were available for 279 of 304 individuals (91.8%).

Secondary Outcome of the Total DSM-IV MDD Symptom Score

A total DSM-IV MDD symptom score defined by the CAPA at follow-up was calculated. This number represented the mean of the total symptoms aggregated across T2 and T3.

Antecedent Variables Assessed at Baseline (T1)

Dimensional Clinical Antecedents

Low Mood | The Mood and Feelings Questionnaire is a widely accepted depression screening instrument and was used to generate a full range of low mood scores.⁴⁰ It includes 34 items about a child's mood symptoms during the past 3 months, rated from 0 (not true) to 2 (true).⁴⁰ Scores across informants were combined by using the highest rating per item from the parent or the child. Internal reliability was excellent ($\alpha = .95$). We did not use the CAPA depression score as a predictor to avoid the possibility of criterion contamination when predicting new-onset MDD at follow-up diagnosed using the CAPA and because the threshold for endorsing an MDD symptom is high.³⁸

Fear/Anxiety | The Screen for Child Anxiety Related Emotional Disorders is a 41-item questionnaire^{41,42} that assesses children's symptoms of anxiety (generalized, panic, somatic, school, separation, and social anxiety), rated from 0 (not true or hardly ever true) to 2 (very true or often true).^{42,43} Internal reliability was excellent ($\alpha = .93$). Parent and child data were combined as above for low mood.

Irritability and Disruptive Behavior | Symptoms of oppositional defiant disorder were assessed with the CAPA. An irritability score was calculated by combining the following items (0 for absent and 1 for present): touchy or easily annoyed, angry or resentful, and temper tantrums.^{44,45} Other items (disobedient or break rules, annoys others, blames others, and spiteful or vindictive) were used to create a disruptive behavior score. The 2 scales showed adequate internal consistency ($\alpha = .61$ for both).

Indexes of the Degree of Familial Risk

Severity of parental MDD^{16,34} and familial loading for MDD in additional family members¹⁷ were used to index the degree of offspring familial risk. Using a life-history calendar,^{35,36} parents reported on any hospitalizations for depression and gave details of their previous worst 2 episodes of depression and associated impairment.⁴⁶ A severe episode of depression was de-

fined as a period of hospitalization due to depression or an episode of depression with severe impairment in at least 1 area of functioning (Global Assessment of Functioning Scale score, ≤ 50).^{34,46} Family history of depression in addition to the index parent was ascertained by asking parents about a diagnosis of depression in first- and second-degree relatives of the child. The number of family members with a history of depression was weighted by relatedness.¹⁷

Social Adversity Indexes

A measure of psychosocial adversity was derived from recent stressful life events.⁴⁷ A total score (maximum, 21) was calculated by summing stressful events occurring within the past 12 months. Sample items include death of a close friend, serious illness, being bullied, and increased quarrelling between parents. If a life event was reported by the parent or the child, it was considered present.⁴⁸

Low parent-reported household income was considered a measure of economic disadvantage and was defined as a gross annual family income of £20 000 (US \$24 368) or less.⁴⁹ In this sample, the amount is equivalent to the international definition of poverty (<60% of the median income).⁵⁰

Statistical Analysis

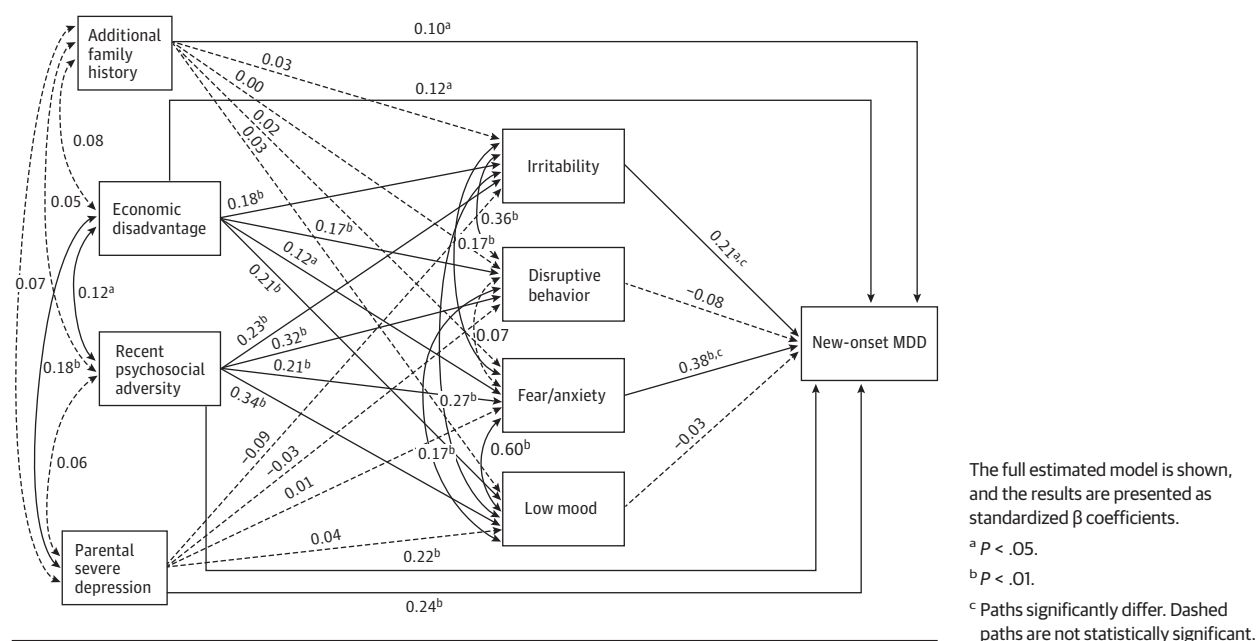
Structural equation modeling, which enables simultaneous assessment of all hypothesized risk paths, was performed. The **Figure** shows the full estimated model, and the results are presented as standardized β coefficients. We hypothesized that irritability, disruptive behavior, fear/anxiety, and low mood would independently represent antecedents, even allowing for correlations between them, given previous evidence for each as a clinical antecedent of MDD.^{21,23,24,26,45} Furthermore, it was hypothesized that indicators of familial risk (parental depression severity and additional family history of depression) and social risk (recent psychosocial adversity and economic disadvantage) would have direct and indirect effects (via the clinical antecedents) on new-onset MDD. Analyses were conducted using a computer program (LISREL, version 8.8, for Windows; Scientific Software International, Inc).⁵¹ A polyserial covariance matrix was estimated (using PRELIS; Scientific Software International, Inc) before analyses because some variables were binary. Three hundred four cases were available. Little test indicated that data were missing completely at random ($\chi^2_{18} = 16.13$, $P = .58$). Full information maximum likelihood estimation enabled the use of all available data. The fit of the final model was excellent ($\chi^2_{10} = 7.75$, $P = .65$; root-mean-square of approximation, 0.00 [95% CI, 0.00-0.05]; Comparative Fit Index, 1.00; and standardized root-mean-square residual, 0.01). Indirect effects were estimated after controlling for the effect of the paths from other risk factors to the clinical antecedents. Analyses were conducted between September 1, 2015, and May 27, 2016.

Results

Primary Analysis

On average, children and adolescents had a mean (SD) of 1.85 (1.74) (range, 0-8.5) DSM-IV symptoms of MDD at follow-up.

Figure. Structural Equation Model Examining Pathways to New-Onset Major Depressive Disorder (MDD)



Twenty (6 males and 14 females) had new-onset MDD, with a mean (SD) age at onset of 14.4 (2.0) years (range, 10-18 years) (Table). Structural equation modeling analysis results for the primary outcome of new-onset offspring MDD are shown in the Figure and are described below.

Dimensional Clinical Antecedents

Irritability was associated with new-onset MDD ($\beta = 0.12$, $P = .03$), as was fear/anxiety ($\beta = 0.38$, $P < .001$). In contrast, allowing for other effects in the full model, neither disruptive behavior ($\beta = -0.08$, $P = .14$) nor low mood ($\beta = -0.03$, $P = .65$) was associated with new-onset MDD. To compare the magnitude of the 2 paths showing significant association with new-onset MDD (irritability and fear/anxiety), we constrained them to be equal, which resulted in a significant χ^2 change ($\chi^2_1 = 9.09$, $P = .003$), indicating that the path from fear/anxiety to new-onset MDD was significantly stronger. The association between irritability and fear/anxiety was low but significant ($\beta = 0.17$, $P = .001$), suggesting that they do not frequently co-occur (Figure).

Indexes of Familial Risk

The direct paths from additional family history of depression to new-onset MDD ($\beta = 0.10$, $P = .03$) and from parental depression severity to new-onset MDD ($\beta = 0.24$, $P < .001$) were significant. Neither of the indexes of familial risk was associated with the clinical antecedents.

Indexes of Social Risk

Both economic disadvantage ($\beta = 0.12$, $P = .02$) and recent psychosocial adversity ($\beta = 0.22$, $P < .001$) had significant direct effects on new-onset MDD. In addition, economic disadvantage and recent psychosocial adversity were associated with the clinical antecedents.

Indirect Effects

We hypothesized that indexes of familial and social risk would influence risk for new-onset MDD indirectly via the dimensional clinical antecedents, as well as directly. None of the indirect effects were significant, including economic disadvantage to new-onset MDD via irritability ($\beta = 0.007$, $P = .32$), economic disadvantage via fear/anxiety ($\beta = -0.012$, $P = .43$), recent psychosocial adversity via fear/anxiety ($\beta = -0.012$, $P = .45$), and irritability ($\beta = 0.003$, $P = .57$).

Secondary Analysis

The CAPA-derived DSM-IV MDD symptoms were assessed as a secondary outcome (eAppendix in the Supplement). The pattern of the results was similar to the findings for the primary outcome. The only exception was that the paths to MDD symptoms from irritability and from fear/anxiety were not significantly different ($\chi^2_1 = 0.27$, $P = .61$). The small number of affected boys (Table) precluded examination of sex differences for new-onset MDD. We thought it important to examine age effects by identifying and excluding prepuberty-onset MDD cases given evidence that they may differ from puberty-onset cases.²² We also considered excluding cases in which irritability was the defining MDD mood symptom. However, there were no such instances (eAppendix in the Supplement). Additional sensitivity analyses (eAppendix in the Supplement) examined which of the separate aspects of fear/anxiety (generalized anxiety, social anxiety, etc) were most associated with new-onset MDD and whether irritability and fear/anxiety predicted an earlier child or adolescent onset. The results suggested that generalized anxiety symptoms were driving the predictive effect of fear/anxiety on new-onset MDD and that fear/anxiety (and not irritability) predicted an especially early MDD onset.

Discussion

In a longitudinal study of children and adolescents at high familial risk of MDD, we examined mechanisms underlying the development of a first episode of adolescent-onset MDD. Simultaneous testing of different pathways suggested 6 routes to adolescent depression (2 via the clinical antecedents and 4 via familial/genetic and social risk factors). Both irritability and fear/anxiety predicted new adolescent-onset MDD and MDD symptom count. These effects were independent of each other, as well as of disruptive behavior and low mood. These antecedents are often examined individually and are correlated. To our knowledge, their joint contribution has not been examined together in this way. The observation that irritability and not other aspects of oppositional behavior increased risk for new-onset MDD is consistent with the results from population-based studies.^{23,26,45,52} Subthreshold low mood symptoms are known to predate depression.^{21,24} Therefore, the finding that fear/anxiety predicted new-onset MDD over and above the effect of low mood may seem surprising, but these dimensions are highly correlated (Figure). While anxiety and depression cross-predict each other over time,^{26,53-59} anxiety typically emerges earlier,²² which may contribute to the stronger predictive effect observed for fear/anxiety on first adolescent-onset MDD. Sensitivity analyses illustrated that generalized anxiety symptoms were driving the predictive effect of fear/anxiety on new-onset MDD. Overall, our findings suggest that also targeting irritability or fear/anxiety^{60,61} as a means of depression prevention in children seems warranted. Investigating the neural or behavioral correlates of irritability and fear/anxiety may help elucidate how these dimensions increase MDD risk.⁶²

We predicted that indicators of familial loading and social risk would influence MDD onset indirectly via effects on dimensional clinical antecedents. We did not find such evidence, and all the indirect paths were nonsignificant. In contrast, there were significant direct effects of all familial/genetic and social risk factors on MDD. Therefore, the indicators of social risk predicted MDD independent of correlated familial risk, parental depression severity, and clinical antecedents in the child. This result has important implications for treatment and prevention and highlights the need to resolve not only clinical phenomena in the child but also wider contextual difficulties. Effective prevention of adolescent MDD is important given the potential for long-term beneficial effects on adult functioning.⁶³ Our findings suggest that primary prevention methods for depression in groups with high familial risk will need to include effective treatment of parental depression,^{30,64,65} irritability, and fear/anxiety in the child and consider social risk factors. Family-based programs may be indicated in children at high familial risk of depression because parental depression is associated with social adversity (poverty and stress exposure)⁶⁶⁻⁶⁸ and moderates the effectiveness of preventive programs focusing on the child.^{30,69} Our results underscore the potent effect of social risks in the initial development of adolescent depression.^{49,66,70,71}

This study has several important strengths, including a large, prospective longitudinal investigation of children and

Table. Descriptive Statistics of Children and Adolescents

Construct	Value
Indicators of Social and Genetic Risk at Baseline	
Additional family history, mean (SD) [range] ^a	0.75 (0.86) [0-6]
Parental severe depression, No./total No. (%) ^{b,c}	205/303 (67.7)
Parental GAF score for worst episode of depression, mean (SD) [range]	42.46 (17.45) [4-90]
Economic disadvantage, No./total No. (%) ^d	80/280 (28.6)
Recent psychosocial adversity, mean (SD) [range] ^e	3.30 (2.30) [0-12]
Dimensional Clinical Antecedents at Baseline, Mean (SD) [Range]	
Irritability	1.33 (1.12) [0-3]
Disruptive behavior	1.51 (1.79) [0-8]
Fear/anxiety	23.49 (14.82) [0-63]
Low mood	18.46 (13.18) [0-62]
Primary and Secondary Outcomes at Follow-up	
New-onset MDD, No./total No. (%)	20/279 (7.2)
Boys	6
Girls	14
Age at onset of new-onset MDD, mean (SD) [range], y	14.4 (2.0) [10-18]
DSM-IV symptoms of MDD, mean (SD) [range]	1.85 (1.74) [0-8.5]

Abbreviations: GAF, Global Assessment of Functioning Scale; MDD, major depressive disorder.

^a Number of first-degree and second-degree relatives with depression weighted by relatedness.

^b A GAF score of 50 or less or hospitalization for depression.

^c Data on parental severe depression missing for 1 case.

^d Gross family income of £20 000 (US \$24 368) or less.

^e Number of recent stressful life events.

adolescents at high familial risk of MDD with repeated measurement using comprehensive psychiatric assessments, allowing a novel focus on incident cases of new-onset MDD, low rates of attrition across assessments, and the use of a method appropriate for simultaneously modeling multiple correlated risk effects. However, the results should be interpreted in light of some considerations and limitations.

Limitations

First, although the rates of MDD were higher than those in comparable community studies,⁵⁶ participants in this sample had not yet reached the peak period of risk for MDD, which occurs in early adult life; therefore, the numbers with MDD are low. However, the findings were replicated for MDD symptom count. Second, we selected the clinical antecedents and indicators of familial and psychosocial risk on the basis of empirical evidence.^{6,8,9,17,20,21,23,26,27,45} It is inevitable that some variables viewed to be important because they are disrupted in major depression (eg, parenting⁷² and neuropsychological or cognitive dysfunction⁷³) will have been omitted. Measurement differences between constructs may also contribute to the results (eg, the clinical antecedent construct of fear/anxiety contained more items than that for irritability). Third,

we cannot rule out person effects on the environment (ie, that individuals to some extent elicit environmental risk exposure through their behavior).^{74,75} However, it seems unlikely that children evoke economic adversity, and evidence suggests causal effects of psychosocial adversity on MDD when accounting for inherited influences on environmental exposure.⁷⁶ Fourth, as would be expected, there were few boys with MDD in the sample, meaning that we were unable to assess sex differences in the pathways to first-onset MDD. Such variations in the pathways to lifetime adult MDD have been reported⁷⁷⁻⁷⁹; therefore, whether there are sex differences in pathways to the incidence of adolescent-onset MDD will require future investigation. Pooled analyses across multiple data sets may be needed to increase sample sizes for such analyses. Fifth, we assessed indicators of familial risk for MDD using data from clinical interviews as opposed to measured genotypes. However, family history provides complementary information to molecular genetic risk scores, which are only

weakly predictive at present.⁸⁰ Sixth, the sample consisted mostly of depressed mothers, making it unclear whether the findings would generalize to the offspring of depressed fathers, which warrants future investigation.

Conclusions

This study of children and adolescents at high familial risk of MDD shows that irritability and fear/anxiety are important clinical antecedents of new-onset MDD but that familial and social risk factors also contribute to risk for the initial onset of adolescent MDD. Primary depression prevention or early intervention strategies may need to not only target clinical features in the high-risk child and the parent but also incorporate public health and community strategies to help overcome social risks, most notably poverty and psychosocial adversity.

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Study concept and design: Rice, A. K. Thapar, Collishaw, Harold, A. Thapar.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rice, Hammerton, Harold, A. Thapar.

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Invited Commentary

Prevention Targets for Child and Adolescent Depression

Anne L. Glowinski, MD, MPE; Max S. Rosen, MD

In this issue of *JAMA Psychiatry*, Rice and colleagues¹ challenge us to prioritize the prevention of child and adolescent depression. As summarized by the authors, the problem is of major public health significance.

The study's major contribution is the examination and elucidation of pathways to first-onset major depressive disorder (MDD) in children and adolescents 9 to 17 years old at high risk



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for depression as indexed by a parental history of at least 2 episodes of MDD. Much extant work has identified those risk factors that place adolescents at highest risk for depression, such as the independent influences of parental depression and low socioeconomic status, both of which increase the hazard ratios 2-fold for adolescent depression.²

Rice and colleagues¹ uncover multiple possible pathways to first-onset MDD, including indirectly through clinical antecedents categorized as fear/anxiety ($\beta = 0.38, P < .001$) and irritability ($\beta = 0.12, P = .03$). Most important, those 2 antecedents have not been used as often as low mood ($\beta = -0.03, P = .65$ in the present study) in prevention trials to indicate high risk, despite some previous evidence that they are phenotypes that indeed predict the development of depression. For example, Whelan and coworkers³ found that postnatal maternal depressive symptoms were associated with adolescent irritability symptoms, which in turn correlated with adolescent depressive symptoms ($\beta = 0.11, P < .05$). Notably, poverty ($\beta = 0.12, P = .02$), severity of parental illness ($\beta = 0.24, P < .001$), and psychosocial adversity ($\beta = 0.22, P > .001$), as measured by a composite score of recent stressful life events, contribute significantly and directly to first-onset MDD.¹ Therefore, the present study will potentially pave the way for better prevention targets in high-risk youth.

It is critical to pause and reflect on the fact that this study also strengthens previous findings that exposure to parental

depression and low socioeconomic status are significant and independent risk factors for youth depression.⁴ Clinicians are typically familiar with the concepts of primary, secondary, and tertiary prevention, but fewer are aware of the paradox by Rose,⁵ which involves understanding the surprising difference between the effect of individual-level (often termed *targeted*) vs population-level (often termed *universal*) prevention approaches. Although population-level risk factors typically have much smaller effect sizes than individual-level risk factors for a given person (eg, an urban environment vs a family history in a first-degree relative as an individual risk factor for schizophrenia), they paradoxically affect a much larger number of people and thus translate into potentially large effect sizes at the population level. This large influence is intuitively not anticipated, especially not by clinicians, who are still largely trained to think about illnesses at individual levels rather than at population levels.

Most reviews of youth depression prevention efforts concur that selective prevention programs (those targeting high-risk individuals) outperform universal intervention programs, which direct efforts at all individuals in a given population. For instance, in their meta-analysis of 32 different depression prevention strategies that mostly used cognitive behavior therapy, stress reduction, and problem-solving techniques, Stice and colleagues⁶ concluded that studies targeting adolescents with depression risk factors, such as negative cognitions or anhedonia, had a moderate effect size on average ($r = 0.23, P < .001$), whereas the mean effect size for universal prevention programs was trivial ($r = 0.04$, not significant). Ahlen and colleagues² explain this finding as predictable because higher-risk adolescents have more room for improvement (hence the larger effects on depressive symptoms of targeted vs universal prevention programs). Although much of the evidence suggests that most of the effect of universal trials is driven by improvement in adolescents with